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EXAMINER	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/585,609	SCHELLER, DIETER	
	Examiner	Art Unit	
	SAVITHA RAO	1614	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on *02 September 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-20* is/are pending in the application.

4a) Of the above claim(s) *19 and 20* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-18* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *11/30/2007*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claims 1-20 are pending.

Claims 19-20 are withdrawn from consideration as being drawn towards a nonelected invention.

Claims 1-18 are under consideration in the instant office action.

Election/Restrictions

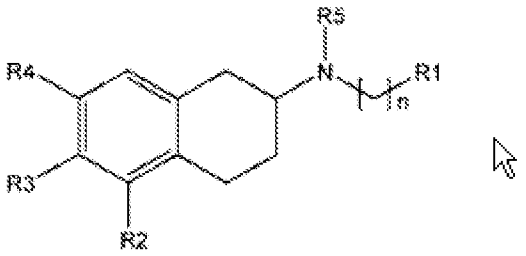
Applicant's election with traverse of Group II (claims 1-18 in part) in the reply filed on 09/02/2008 is acknowledged. The traversal is on the ground(s) that Examiner finds the applicant's argument not persuasive. Even without using the reference to break the unity, the groups possess lack of unity for the following reasons:

(a) Groups I and II, although patentably distinct, do indeed comply with the unity of invention requirement of PCT Rule 13, since the claims of Groups I and II (Claims 1-18) share as a common technical feature more than just a compound of the above formula, but a method for preventive treatment of Parkinson's disease comprising administering such a compound to a subject. The Examiner's definition of the core technical feature apparently fails to recognize that the claims of Groups I and II are method-of-use claims for a recognized class of chemical compounds. Thus, any special technical feature analysis under PCT Rule 13.2 should include not only the chemical formula above, but also administration to a subject for preventive treatment of Parkinson's disease

Examiner acknowledges Applicants arguments and finds the argument persuasive. Examiner is hereby establishing a new restriction requirement where in previously

restricted Groups I and II are rejoined together and Groups III and IV are rejoined as follows with a modified rationale provided to demonstrate lack of unity.

Group I: Claims 1-18 are drawn to method for preventive treatment of Parkinson's disease in a subject comprising administering to the subject a compound of formula

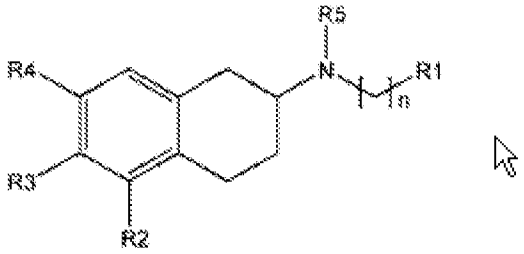


Group II: Claim 19-20 are drawn to a kit for diagnosis and treatment of Parkinson's disease comprising a diagnostic agent and a pharmaceutical formulation of a compound of general formula shown above.

An international application should relate to only one invention or, if there is more than one invention, the inclusion of those inventions in one international application is only permitted if all inventions are so linked as to form a single general inventive concept (PCT Rule 13.1). With respect to a group of inventions claimed in an international application, unity of invention exists only when there is a technical relationship among the claimed inventions involving one or more of the same or corresponding special technical features. The claims herein lack unity of invention under PCT rule 13.1 and 13.2 since, under 37 CFR 1.475(a).

Groups I and II lack unity of invention under 37 CFR 1.475 since the two groups (I-II) are not unified by the same or corresponding special feature as detailed below

The special technical feature in Group I is the method of preventive treatment of Parkinson's disease comprising administering to a subject a compound of formula shown



Accordingly, the method involves the steps of identification of patients at risk of Parkinson's disease, diagnostic determination of early signs of Parkinson's disease, reviewing the symptoms, understanding the underlying cause of the symptoms and analysis of the physiological/biochemical causes of the disease, diagnosis, dosage and route of administration determination and the actual process of treating such a drug to the patient including monitoring of prognosis to see if the progression or onset of the disease has been prevented.

The special technical feature in Group II which is a kit for diagnosis and treatment of Parkinson's disease comprising a diagnostic agent and a pharmaceutical formulation of a compound of general formula. The special technical feature of this Group is that it comprises of a **diagnostic agent** in addition to the compound, the kit comprises of all the reagents necessary for diagnosis of Parkinson's disease. The kit is used specifically for diagnosis and treatment of Parkinson's disease (not prevention

Accordingly there is no same or corresponding special technical features unifying Groups I and II and thereby they lack unity.

Therefore, since in the instant application the claims are drawn to distinct inventions, based on, composition and method of using the compositions as shown above, and according to 37 CFR 1.475(e): the determination whether a group of inventions is so linked as to form a single general inventive concept shall be made without regard to whether the inventions are claimed in separate claims or as alternatives within a single claims.

The claims, therefore, lack unity of invention.

Since applicant elected Group II from the restriction requirement set forth on 06/09/2008, the elected Group II is encompassed within Group I of the new restriction requirement set for the above**. Accordingly, the instant application will be examined with respect to the elected invention of Group I set forth above**.

Applicant's election of a single specie of compound “Rotigotine” administered in the method of preventive treatment of Parkinson’s with traverse. The traversal is on the grounds that the individual species embraced by claims 1-20 while patentably distinct, are sufficiently closely related to each other not to impose undue search burden on the examiner. Examiner finds the applicant’s argument unpersuasive and maintains the election requirement as they are patentably distinct (as admitted by the applicant on page 5 of the response to requirement) and independent and accordingly lack unity. The claims are directed to patentably distinct species and, thus, do not constitute overlapping subject matter that would result in a coextensive search. **Claims 1-18 will be examined as it reads on the elected species of Rotigotine**.

Accordingly, claim 19-20 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on 06/09/2008.

Restriction for examination purposes as indicated is proper. However, the restriction is not made final and would be made final in the next office action.

Claim Rejections - 35 USC § 112

(Enablement)

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-18 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the method of "**treatment** of Parkinson's disease in a subject", does not reasonably provide enablement for the "**preventive** treatment" of a subject". The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

Attention is directed to In re Wands, 8 USPQ2d 1400 (CAFC 1988) at 1404 where the court set forth the eight factors to consider when assessing if a disclosure would have required undue experimentation. Citing Ex parte Forman, 230 USPQ 546 (BdApls 1986) at 547 the court recited eight factors:

1) the quantity of experimentation necessary, 2) the amount of direction or guidance provided, 3) the presence or absence of working examples, 4) the nature of the invention, 5) the state of the prior art, 6) the relative skill of those in the art, 7) the predictability of the art, and 8) the breadth of the claims.

The instant specification fails to provide guidance that would allow the skilled artisan to practice the instant invention without resorting to undue experimentation, as discussed in the subsections set forth herein below.. All of the **Wands factors** have been considered with regard to the instant claims, with the most relevant factors discussed below.

1. **Nature of the Invention**:

All of the rejected claims are drawn to a method of preventive treatment of Parkinson's disease comprising administering to the subject rotigotine. The nature of the invention is extremely complex in that it encompasses the actual **prevention** of a neurodegenerative disease such that the subject treated with rotigotine does not contract Parkinson's disease.

2. Breath of the Claims*:*

The complex nature of the claims greatly exacerbates by breath of the claims. The claims encompass prevention of a complex cell degenerative disorder in humans which has potentially many different causes (i.e. many different mutations or combination of mutations), each of which may or may not be addressed by the administration of rotigotine. The term **preventive treatment** is very broad and is inclusive of **prevention** of Parkinson's disease in subjects who display early symptoms

of the disease and **prevention** the onset of preclinically evident stage of Parkinson's disease in subjects at risk . In other words the instant claim is drawn to preventive treatment of all preclinical stages and all stages of the Parkinson's disease including any undetectable stages of Parkinson's.

3. **Guidance of the Specification:**

The guidance given by the specification as to how one would administer the claimed compounds to a subject in order to actually prevent Parkinson's disease is minimal. All of the guidance provided by the specification is directed towards **treatment rather than prevention** of Parkinson's disease.

4. **Working Examples:**

All of the working examples provided by the specification are directed toward the treatment rather than prevention of Parkinson's disease. Both embodiment 3 [0077] and embodiment 4 [0078] recited on page 16 of the instant disclosure describe the effect of rotigotine in mice displaying clinical manifestations of neurodegeneration. Based on the state of the art as discussed below, this data is insufficient to demonstrate the preventive action of rotigotine.

5. **State of the Art :**

While the state of the art is relatively high with regard to **treatment** of neurodegenerative disorders (i.e. Parkinson's disease), the state of the art with regard to **prevention** of such disorders is underdeveloped. In particular, there do not appear to be any examples or teachings in the prior art wherein a compound similar to the claimed compounds was administered to a subject to **prevent** development of

Parkinson's disease. Preventive treatment requires preclinical detection of Parkinson's disease. As taught by Stern et al (Annals of Neurology, Vol 56, No 2, 2004, pages 169-170, Referenced in the instant IDS), choosing the "right" clinical end point, the most appropriate patient populations, study design and possible surrogate end points have challenged modern Parkinson's disease experimental therapeutics. Stern teaches that there is a lengthy preclinical phase of the disease in which the degenerative process proceeds long before clinically recognizable symptoms emerge (page 169, left col., 3rd paragraph). Although the preclinical testing for Parkinson's disease is within reach, there are several complex implication associated with the technology and the first being identification of the population who has to be screened for the disease, genetic factor, environmental factors and /or occupational exposure might prompt screening with possible legal implications, furthermore Stern teaches that neurodegenerative disease delay or prevention would need to be embraced by health insurers as a worth (reimbursable) goal in that the preclinical diagnosis of Parkinson's disease is only ready when there is something to offer in terms of cure for the affected individual (page 170, left col. 5th paragraph to right col. 1st paragraph). Stern additionally states that although numerous compounds prevent cell loss in laboratory models of neurodegeneration, demonstrating their effect in acceptable clinical trials has been a challenge (page 170, right col., 2nd paragraph).

Tuite et al (Expert opinion in investigational Drugs, 12(8), pages: 1335-1352, 2003, referenced in the instant IDS) teaches that there is presently no cure for Parkinson's disease, although several agents are routinely used to manage symptoms

(page 1335, 1st paragraph) .**Tuite also teaches that although effective, the overall impact of symptomatic medications is limited in the long run, since there is no means to prevent Parkinson's disease (i.e. preventive therapy), alter its progression (i.e. neuroprotective therapy) or restore lost dopamine neurons (i.e. restorative therapy)** (page4 1336, left col. 2nd paragraph).

6. **Predictability of the Art:**

The lack of significant guidance from the specification or prior art with regard to the actual **prevention** of Parkinson's disease in a human subject with the claimed compounds makes practicing the claimed invention unpredictable in terms of **prevention** of Parkinson's disease.

7. **The amount of Experimentation Necessary:**

In order to practice claimed invention, one of skilled in the art would have to first envision a combination of appropriate pharmaceutical carrier, compound dosage, duration of treatment, route of administration, etc. and appropriate animal model system for one of the claimed compounds and test the combination in the model system to determine whether or not the combination is effective for prevention of Parkinson's disease. If unsuccessful, which is likely given the lack of significant guidance from the specification or prior art regard prevention of Parkinson's disease with any compound, one of skill in the art would have to then either envision a modification of the first combination of pharmaceutical compound, compound dosage, duration of treatment, route of administration, etc. and appropriate animal model system, or envision an entirely new combination of the above, and test the system again. If again

unsuccessful, which is likely given the lack of significant guidance form the specification of prior art regarding prevention of Parkinson's disease with any compound, the entire, unpredictable process would have to be repeated until successful. Therefore, it would require undue, unpredictable experimentation to practice the claimed invention to prevent the development of Parkinson's disease in a subject by administration of the claimed compounds.

Therefore, a method of preventive treatment of Parkinson's disease comprising administering to a subject is not considered to be enabled by the instant specification.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1, 5-14, 17, 18 are rejected under 35 U.S.C. 102(b) as being anticipated by Tuite et al (Expert opinion in investigational Drugs, August, 12(8), pages: 1335-1352, 2003. referenced in Instant IDS)

Tuite reviews recent developments in the pharmacological treatment of Parkinson's disease. Tuite discloses Rotigotine as a selective D2 receptor agonist that is currently in Phase II and III clinical trials (PATCH study). The study was conducted to compare efficacy, safety and tolerability of four doses of

rotigotine (4.5 mg, 9 mg, 13.5 mg, 18 mg) and all doses were delivered using up to four patches. Tuite teaches that in Phase III double-blind, randomized placebo controlled parallel group clinical trials was conducted in 316 patients with early stages of Parkinson's disease. The primary end point was a change from baseline in UPDRS part II (ADL) and III (motor) scores at week 11 of treatment and the secondary end points included UPDRS mental, ADL and motor subscale scores and the Hoehn and Yahr stage from baseline to week 11. Rotigotine produced linear and dose related improvement in UPDRS scores relative to baseline up to a dose of 13.5 mg. In summary Tuite teaches that this rotigotine patch study produced a statistically significant reduction of combined ADL and motor scores in Parkinson's disease subjects (page 1342, left col., Last paragraph to right col., 1st paragraph). Tuite additionally discloses that Rotigotine, a dopamine agonist delivered transdermal, delivers steady-state plasma concentrations within 24 hours of patch application and may be beneficial as adjunctive therapy in patients with motor fluctuations and rotigotine appears to be efficacious as monotherapy in de novo patients (early stage Parkinson's) (page 1354, right col. Last paragraph to page 1343, left col., 1st paragraph).

In individuals with idiopathic PD, approximately 60% of the nigrostriatal neurons of the substantia nigra (SN) are degenerated before neurologists can establish the diagnosis as evidenced by Becker et al (abstract) Accordingly, all the individuals in the study recited by Tuite who had early stages of PD inherently had approximately 60% loss of the substantia nigra. The instant claim 14, recites the limitation less than 60%

and absence of the actual range which defines the term "less than" the term approximately anticipates the limitation. In accordance with MPEP §2131.01, it is proper to rely upon a secondary reference for a rejection under 35 U.S.C. 102, provided that the additional reference is relied upon to demonstrate that a characteristic or property not disclosed by the primary reference is, in fact, inherent.

Claims 1, 5-13, 14-18 are rejected under 35 U.S.C. 102(b) as being anticipated by Shoulson (Principal investigator) et. al. (Archives Neurology, Vol. 60, December 2003, 1721-1728, Published 2nd Monday of the month which would be 12/13/2003)

Shoulson (principal investigator as recited on page 1726) and his study group disclose a controlled trial of Rotigotine Monotherapy in Early Parkinson's Disease (PD). The study was conducted to determine the efficacy, safety, and tolerability of rotigotine in patients with early PD who required but were not yet receiving other dopaminergic therapy (abstract). Eligible subjects for the study included men and women older than 30 years who were diagnosed as having idiopathic PD and had a Hoehn and Yahr stage of 3 or less. The placebo-controlled clinical trial demonstrated that rotigotine administered transdermally at dosages ranging from 4.5 to 18.0 mg/d was safe and generally well tolerated for up to 11 weeks in subjects with early PD. The study also defined the minimum effective dosage of rotigotine in the 9.0- to 13.5-mg range and demonstrated a dose-response relationship among the active treatment groups up to 13.5 mg, with a plateau in the therapeutic effect occurring between 13.5 and 18.0 mg. Transdermal rotigotine treatment produced clinical improvement in parkinsonian

symptoms (as measured by the change in motor and ADL UPDRS score between baseline and 11 weeks of treatment) comparable to that reported after administration of the dopamine agonists pramipexole and ropinirole. Table 1 on page 1724 lists the baseline characteristics by treatment groups where patients with UPDRS score for mental and ADL at less than 10. Additionally this study confirms the preliminary data that a dopamine agonist can be effectively and safely delivered via transdermal administration.

In individuals with idiopathic PD, approximately 60% of the nigrostriatal neurons of the substantia nigra (SN) are degenerated before neurologists can establish the diagnosis as evidenced by Becker et al (abstract) Accordingly, all the individuals in Shoulson's study who had idiopathic PD inherently had approximately 60% loss of the substantia nigra. The instant claim 14, recites the limitation less than 60% and absence of the actual range which defines the term "less than" the term approximately anticipates the limitation. In accordance with MPEP §2131.01, it is proper to rely upon a secondary reference for a rejection under 35 U.S.C. 102, provided that the additional reference is relied upon to demonstrate that a characteristic or property not disclosed by the primary reference is, in fact, inherent.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-18 are rejected under 35 U.S.C. 103(a) as being unpatentable over Tuite et al (Expert opinion in investigational Drugs, 12(8), pages: 1335-1352, 2003) as evidenced by Becker et al.(J. Neuorol., 249(suppl.3) III/40-III/48, 2002, referenced in instant IDS) further in view of Double et al. (WO 02/31499, referenced in instant IDS) and Guttman (Canadian Medical Association Journal, 168 (3), 2003, 293-301, referenced in instant IDS)

Tuite reviews recent developments in the pharmacological treatment of Parkinson's disease (PD). Tuite discloses Rotigotine as a selective D2 receptor agonist that is currently in Phase II and III clinical trials (PATCH study). The study was conducted to compare efficacy, safety and tolerability of four doses of rotigotine (4.5 mg, 9 mg, 13.5 mg, 18 mg) and all doses were delivered using up to four patches. Tuite teaches that in Phase III double-blind, randomized placebo controlled parallel group clinical trials was conducted in 316 patients with early stages of Parkinson's disease. The primary end point was a change from baseline in UPDRS part II (ADL) and III (motor) scores at week 11 of treatment and the secondary end points included UPDRS mental, ADL and motor subscale scores and the Hoehn and Yahr stage from baseline to week 11. Rotigotine produced linear and dose related improvement in UPDRS scores relative to baseline up to a dose of 13.5 mg. In summary Tuite teaches that this rotigotine patch study produced a statistically significant reduction of combined ADL and motor scores in Parkinson's disease subjects (page 1342, left col., Last paragraph to right col., 1st paragraph). Tuite additionally discloses that Rotigotine, a dopamine agonist delivered transdermal, delivers steady-state plasma concentrations within 24 hours of patch application and may be beneficial as adjunctive therapy in patients with motor fluctuations and rotigotine appears to be efficacious as monotherapy in de novo patients (early stage Parkinson's) (page 1354, right col. Last paragraph to page 1343, left col., 1st paragraph). Tuite additionally teaches in a study in subjects with advanced PD no significant difference between rotigotine and placebo was observed (page 1343, left col. , 3rd paragraph) and that rotigotine use in advanced PD

patients also requires additional medications to alleviate symptoms, which may include concurrent orally administered dopamine agonists (page 1343, left col., 1st paragraph).

In individuals with idiopathic PD, approximately 60% of the nigrostriatal neurons of the substantia nigra (SN) are degenerated before neurologists can establish the diagnosis as evidenced by Becker et al (abstract) Accordingly, all the individuals in clinical trail described by Tuite with early PD of inherently had approximately 60% loss of the substantia nigra. The instant claim 14, recites the limitation less than 60% and absence of the actual range which defines the term "less than" the term approximately anticipates the limitation.

Tuite et al do not specifically recite the presence of at least three of the four cardinal symptoms of Parkinson's disease and is silent to the involvement of mutation in the PARK gene and/or modifications to the alpha synuclein or neuromelanine pattern.

Double et al. teaches the method of detecting neurodegenerative diseases such as Parkinson's disease in a subject comprising testing the subject for an indicator of release of neuromelanin from cells in the brain (abstract). Double et al also teaches that in classical or idiopathic Parkinson's disease at least 65% of total substantia nigral dopaminergic neurons are lost prior to onset of the classical clinical symptoms of the disease and the triad of motor symptoms, tremor, rigidity and bradykinesia typify the onset of the clinical phase of the disease during which the rate of loss of the remaining 35% of dopaminergic cells is significantly slower than during the preclinical phase (page 7, lines 13-17) Double et. al. teaches that neuromelanin is a complex polymer pigment believed to be formed from oxidized dopamine products within the dopaminergic

neurons of the substantia nigra and neuromelanin usually occurs as granule which can be seen in the cell body, but as a consequence of cell death neuromelanin is released into the extracellular space (oage2, lines 4-9). Double et al provides a method of detecting a neurodegenerative disease in a subject comprising testing the subject for an indicator release of neuromelanin cells in the brain, wherein a positive test is indicative of death of brain cells containing neuromelanin and is characterized by an elevated level of the indicator of release of neuromelanin compared to control values (page 2, lines 10-14). Double et al. additionally teaches that the identification of this specific marker provides a means for detecting the disorders characterized by the death of these cells, even prior to the onset of clinical symptoms (page 2, lines 15-17).

Guttman et al. teaches that Parkinson's disease is a progressive neurological disorder characterized by rest tremor, bradykinesia, rigidity and postural instability and the cause is unknown but evidence suggests that it may be due to a combination of environmental and genetic factors (abstract). Guttman teaches that eight genetic loci for monogenic forms of Parkinson's disease have been reported (page 295, left col. 2md paragraph and table 2).Guttman further teaches that in autosomal dominant Parkinson's disease 2 missense mutations in the α-synuclein gene (PARL1) were identified and in pedigree's with autosomal recessive early onset parkinsonism, a wide variety of mutations in the parkin gene (PARK2) were found in about 59% of the families, in which at least one of the affected siblings developed symptoms at or before 45 years of age (page 295, left col., 2nd paragraph). Finally, in table 2 Guttman lists the genetically defined forms of Parkinson's disease and parkinsonism which involves gene mutations

PARK genes 1-8 with their specific Gene involved and its clinical characteristics (page 296, table 2).

It would have been obvious to one of ordinary skill in the art to employ rotigotine in prophylactic treatment of Parkinson's disease because rotigotine is effective for the treatment of Parkinson's disease as taught by Tuite et al early stages of the disease. Moreover, Tuite teaches that rotigotine did not show statistically significant improvement in advanced PD and will have to be administered with other drugs in advanced PD. Becker, Double et al and Guttman et al teaches the various diagnostic parameters in determining the onset of Parkinson's disease. With regard to the specified subject population not exhibiting symptoms of Parkinson, but having a high risk set forth in claims 2 not yet having at lest three of four cardinal symptoms including bradykinesia, resting tremors, rigor etc..; a patient having one or more clinical symptoms including movement anomalies set forth in claim 3 a mutation in PARK-gene set forth and/or alternations in the alpha-synuclein or neuromelanin pattern set forth in claim 4; a loss of less than 60% of dopaminergic cells in the substantial nigra set forth in claim 14; a UPDRS score of less than 10 set forth in claim 15; and a Hohn-Yahr score of 0 or 1 set forth in claim 16, they are all obvious because they are all the current evaluation parameters for determining the stages and diagnostic assessment of Parkinson's disease as well known by the above references. One of ordinary skill in the art would promptly evaluate those patients at risk or in at early stages of Parkinson's disease in order to avoid failing of treating Parkinson's disease at their advanced stage. Accordingly, an ordinarily skilled artisan would be motivated to develop a method of

treatment of Parkinson's disease at its early stages with rotigotine with a reasonable expectation of success since it has been shown to provide effective decrease in the progression of disease as evidenced by the clinical trials in the prior art.

Claims 1-18 are rejected under 35 U.S.C. 103(a) as being unpatentable over Shoulson et al (Principal investigator) et al (Archives Neurology, Vol. 60, December 2003, 1721-1728) , as evidenced by Becker et al.(J. Neuorol., 249(suppl.3) III/40-III/48, 2002, referenced in instant IDS) further in view of Double et al. (WO 02/31499, referenced in instant IDS) and Guttman (Canadian Medical Association Journal, 168 (3), 2003, 293-301, referenced in instant IDS)

Shoulson (principal investigator as recited on page 1726) and his study group teach a controlled trial of Rotigotine Monotherapy in Early Parkinson's Disease (PD). The study was conducted to determine the efficacy, safety, and tolerability of rotigotine in patients with early PD who required but were not yet receiving other dopaminergic therapy (abstract). Eligible subjects for the study included men and women older than 30 years who were diagnosed as having idiopathic PD and had a Hoehn and Yahr stage of 3 or less. The placebo-controlled clinical trial demonstrated that rotigotine administered transdermally at dosages ranging from 4.5 to 18.0 mg/d was safe and generally well tolerated for up to 11 weeks in subjects with early PD. The study also defined the minimum effective dosage of rotigotine in the 9.0- to 13.5-mg range and demonstrated a dose-response relationship among the active treatment groups up to 13.5 mg, with a plateau in the therapeutic effect occurring between 13.5 and 18.0 mg.

Transdermal rotigotine treatment produced clinical improvement in parkinsonian symptoms (as measured by the change in motor and ADL UPDRS score between baseline and 11 weeks of treatment) comparable to that reported after administration of the dopamine agonists pramipexole and ropinirole. Table 1 on page 1724 lists the baseline characteristics by treatment groups where patients with UPDRS score for mental and ADL at less than 10 were treated. Additionally this study confirms the preliminary data that a dopamine agonist can be effectively and safely delivered via transdermal administration. Shoulson additionally teaches that an initial trial of rotigotine in patients with advanced PD with motor fluctuations showed a reduction in off time in treated subjects, but the magnitude of change failed to reach statistical significance when compared with placebo.

In individuals with idiopathic PD, approximately 60% of the nigrostriatal neurons of the substantia nigra (SN) are degenerated before neurologists can establish the diagnosis as evidenced by Becker et al (abstract) Accordingly, all the individuals in Shoulson's study with idiopathic PD of inherently had approximately 60% loss of the substantia nigra. The instant claim 14, recites the limitation less than 60% and absence of the actual range which defines the term "less than" the term approximately anticipates the limitation.

Shoulson et al do not specifically recite the presence/absence of at least three of the four cardinal symptoms of Parkinson's disease and is silent to the involvement of mutation in the PARK gene and/or modifications to the alpha synuclein or neuromelanine pattern.

Double et al. teaches the method of detecting neurodegenerative diseases such as Parkinson's disease in a subject comprising testing the subject for an indicator of release of neuromelanin from cells in the brain (abstract). Double et al also teaches that in classical or idiopathic Parkinson's disease at least 65% of total substantia nigral dopaminergic neurons are lost prior to onset of the classical clinical symptoms of the disease and the triad of motor symptoms, tremor, rigidity and bradykinesia typify the onset of the clinical phase of the disease during which the rate of loss of the remaining 35% of dopaminergic cells is significantly slower than during the preclinical phase (page 7, lines 13-17) Double et. al. teaches that neuromelanin is a complex polymer pigment believed to be formed from oxidized dopamine products within the dopaminergic neurons of the substantia nigra and neuromelanin usually occurs as granule which can be seen in the cell body, but as a consequence of cell death neuromelanin is released into the extracellular space (oage2, lines 4-9). Double et al provides a method of detecting a neurodegenerative disease in a subject comprising testing the subject for an indicator release of neuromelanin cells in the brain, wherein a positive test is indicative of death of brain cells containing neuromelanin and is characterized by an elevated level of the indicator of release of neuromelanin compared to control values (page 2, lines 10-14). Double et al. additionally teaches that the identification of this specific marker provides a means for detecting the disorders characterized by the death of these cells, even prior to the onset of clinical symptoms (page 2, lines 15-17).

Guttman et al. teaches that Parkinson's disease is a progressive neurological disorder characterized by rest tremor, bradykinesia, rigidity and postural instability and

the cause is unknown but evidence suggests that it may be due to a combination of environmental and genetic factors (abstract). Guttman teaches that eight genetic loci for monogenic forms of Parkinson's disease have been reported (page 295, left col. 2md paragraph and table 2).Guttman further teaches that in autosomal dominant Parkinson's disease 2 missense mutations in the α-synuclein gene (PARK1) were identified and in pedigree's with autosomal recessive early onset parkinsonism, a wide variety of mutations in the parkin gene (PARK2) were found in about 59% of the families, in which at least one of the affected siblings developed symptoms at or before 45 years of age (page 295, left col., 2nd paragraph). Finally, in table 2 Guttman lists the genetically defined forms of Parkinson's disease and parkinsonism which involves gene mutations **PARK genes 1-8** with their specific Gene involved and its clinical characteristics (page 296, table 2).

It would have been obvious to one of ordinary skill in the art to employ rotigotine in prophylactic treatment of Parkinson's disease because rotigotine is effective for the treatment of Parkinson's disease as taught by Shoulson et al early stages of the disease. Moreover, Shoulson teaches that rotigotine did not show statistically significant improvement in advanced PD and will have to be administered with other drugs in advanced PD. Becker, Double et al and Guttman et al teaches the various diagnostic parameters in determining the onset of Parkinson's disease. With regard to the specified subject population not exhibiting symptoms of Parkinson, but having a high risk set forth in claims 2 not yet having at lest three of four cardinal symptoms including bradykinesia, resting tremors, rigor etc..; a patient having one or more clinical symptoms

including movement anomalies set forth in claim 3 a mutation in PARK-gene set forth and/or alternations in the alpha-synuclein or neuromelanin pattern set forth in claim 4; a loss of less than 60% of dopaminergic cells in the substantial nigra set forth in claim 14; a UPDRS score of less than 10 set forth in claim 15; and a Hohn-Yahr score of 0 or 1 set forth in claim 16, they are all obvious because they are all the current evaluation parameters for determining the stages and diagnostic assessment of Parkinson's disease as is well known and taught in above references. One of ordinary skill in the art would promptly evaluate those patients at risk or in at early stages of Parkinson's disease in order to avoid failing of treating Parkinson's disease at their advanced stage. Accordingly, an ordinarily skilled artisan would be motivated to develop a method of treatment of Parkinson's disease at its early stages with rotigotine with a reasonable expectation of success since it has been shown to provide effective decrease in the progression of disease as evidenced by the clinical trials in the prior art.

Double Patenting (anticipatory/obvious)

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1-18 are provisionally rejected on the ground of nonstatutory double patenting over claims 15-24 of copending Application No. 11060997 (copending '997). This is a provisional double patenting rejection since the conflicting claims have not yet been patented. The subject matter claimed in the instant application is fully disclosed in the referenced copending application and would be covered by any patent granted on that copending application.

The referenced copending application claims a method for treatment or prophylaxis of dopaminergic cell loss associated with Morbus Parkinson's, comprising administration of rotigotine to the subject, wherein the subject is either an (a) individual not exhibiting symptoms but having a high risk of developing Morbus Parkinson or individual not exhibiting symptoms but having a high risk of developing Morbus Parkinson or an individual for whom three of the four cardinal symptoms of Parkinson is not yet present or only partially present. ('997 claims 15-17), Co-pending '997 also discloses the method of treatment or prophylaxis where in the subject exhibits a mutation in a PARK-gene and/or alteration in the alpha-synuclein or neuromelanin pattern, loss of 60% of dopaminergic cells in the substantia nigra prior, has an UPDRS score of less than 9 and has a Hohn-Yahr score of 0-1 ('997, claims 19-22). Co-pending '997 further discloses that the method comprises administration of rotigotine

either by parenteral, transdermal or mucosal administration at a dose of 0.05-50 mg/day ('997, claims 23-24). Morbus Parkinson's is a specie of Parkinson's disease instantly claimed and accordingly, the co-pending '997 claims anticipates the instant claims.

Although the conflicting claims (claims 1-18 in the instant application and claims 15-24, of the co-pending application 11060997) are not identical as stated above, they are not patentably distinct from each other because the claims of the '997 application fully discloses the instantly claimed method of preventive treatment of Parkinson's disease comprising administering to the subject rotigotine.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claims 1, 5-13 and 17-18 are provisionally rejected on the ground of nonstatutory double patenting over claims 8, 11, and 14 of copending Application No. 10593964 (copending '964). This is a provisional double patenting rejection since the conflicting claims have not yet been patented. The subject matter claimed in the instant application is fully disclosed in the referenced copending application and would be covered by any patent granted on that copending application.

The referenced copending application claims a method for prevention and/or treatment of a Parkinson's plus syndrome comprising administering to a patient a compound selected from the group consisting of rotigotine, its salts or prodrugs ('964, claim 1). Co-pending '964 discloses a method where in the compound rotigotine is administered orally, parenterally, transdermally or transmucosally ('964, claim 11) and

finally co-pending '964 discloses the method wherein the compound rotigotine is administered to provide a dosage of 0.05 mg to 50 mg/ day ('964, claim 14) .

Although the conflicting claims (claims 11, 5-13 and 17-18 in the instant application and claims 1,11 and 14 of the co-pending application 10593964 are not identical as stated above, they are not patentably distinct from each other because the claims of the '964 application fully discloses the subject matter of instant claims 1, 5-13 and 17-18. This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Conclusion

Claims 1-18 are rejected. No claims are allowed

Any inquiry concerning this communication or earlier communications from the examiner should be directed to SAVITHA RAO whose telephone number is (571)270-5315. The examiner can normally be reached on Mon-Fri 7 am to 4 pm..

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ardin Marschel can be reached at 571-272-0718. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/SAVITHA RAO/
Examiner, Art Unit 1614

/Ardin Marschel/
Supervisory Patent Examiner, Art Unit 1614